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NIADDK 1985

Kidney, Urology and Hematology

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES · Public Health Service · National Institutes of Health

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Prepared by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services in January 1985 in connection with Fiscal Year 1986 appropriation hearings.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

KIDNEY, UROLOGY, AND HEMATOLOGY

Kidney and urinary tract diseases affect over 13 million Americans and account for more than 80,000 deaths each year. The Federal Government spends almost $2 billion each year to provide maintenance dialysis and kidney transplantations for more than 70,000 patients with end-stage renal disease. It is anticipated that by 1986, more than 89,000 patients in this country will be kept alive with some form of chronic dialysis. The total annual cost of these treatments has been projected to exceed $2.8 billion.

Urinary tract infections are the second most common bacterial disease treated by physicians, and at least 8,000 patients die each year from infections of the kidney. More than a million Americans per year are hospitalized for the treatment of kidney and urinary tract stones. Approximately 270,000 prostatectomies are performed in the U.S. each year for the relief of urinary obstruction caused by the enlargement of the prostate gland, which occurs in many men over age 40. The total cost of diagnostic procedures and treatment of this disorder alone exceeds $1 billion per year in the U.S.

The economic cost of blood diseases in the U.S. is in excess of $25 billion each year. The annual cost of lost productivity due to blood disorders is estimated to be nearly $3 billion, and deaths from these disorders total several hundred thousand annually.

KIDNEY AND URINARY TRACT DISEASE RESEARCH

The goals of NIADDK's Division of Kidney, Urologic and Hematologic Diseases include prevention, early diagnosis, and treatment of kidney disease through development of an

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understanding of the basic mechanisms and causes of renal and urologic disorders. Areas of study include glomerulonephritis, interstitial nephritis, kidney and bladder stones, polycystic kidney disease, diabetic nephropathy, analgesic-associated and other toxic nephropathies, immune disorders of the kidney, benign prostatic hyperplasia, and numerous other disorders. Chronic renal disease and end-stage kidney disease (ESRD) are two other important target areas, as NIADDK-supported scientists seek ways to reduce the number of patients dependent on dialysis or renal transplantation to compensate for lost kidney function. Other goals include delineation of the basic cause of kidney stones, development of effective treatment for patients suffering with kidney stones, and the design of rational approaches to prevent the occurrence of kidney stones.

Withdrawal of Mixed Analgesics Suggested by NIADDK Consensus Development Panel

"Serious consideration" should be given to the withdrawal of products containing combinations of some common analgesics from over-the-counter use in the United States, according to an NIH consensus development panel that met this year. The products involved are those containing mixtures of aspirin, acetaminophen, salicylamide, or salts of salicylates.

The panel said there is no evidence that single-ingredient painkillers, used as recommended, are related to analgesic kidney disease. Large doses of combined analgesics, however, taken over a long period cause a specific form of disease (analgesic nephropathy) and can lead to chronic kidney failure.

The cost of treatment of patients with end-stage renal disease caused by analgesic nephropathy is estimated to be at least $40 million annually in the U.S. Moreover, for every patient whose kidneys fail, many other habitual users of combination painkillers develop milder forms of the disorder. The consensus panel called analgesic kidney disease "a potentially treatable and preventable disorder" and outlined further areas of research that are needed.

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Kidney Failure Prevented in Lupus Nephritis Patients

Lupus nephritis, a serious, slowly progressive kidney disease, is a potentially fatal complication of lupus (systemic lupus erythematosus), a chronic inflammatory disease of the connective tissue that affects 500,000 Americans, primarily young women. Scientists have thought that an improved survival rate for these patients was due in part to improved treatments with steroids and with cytotoxic drugs, which suppress the autoimmune (abnormal immune response) component of the disease. However, proof that such drugs prevent progression of lupus nephritis has been lacking. So has conclusive evidence that the cytotoxic drugs azathioprine and cyclophosphamide are more effective than conventional steroid therapy.

New evidence that cytotoxic drug therapy effectively prevents progressive failure of the kidneys in patients with lupus nephritis has been reported by NIADDK intramural researcher Dr. James E. Balow and his associates. Results of the long-term, prospective therapeutic trial of conventional and experimental drug regimens show that both prednisone and cytotoxic agents help reduce the likelihood of kidney failure in patients with lupus nephritis.

The researchers conclude that patients treated with cytotoxic drugs face a significantly reduced risk of progressive kidney damage compared to patients treated only with steroids. Dr. Balow and his associates are continuing their studies to determine optimal regimens of these drugs to maximize their value in treatment of lupus nephritis.

Cyclosporine Prevents Rejection in Kidney Transplantation

Kidney transplantation has become increasingly successful due to advances in surgical techniques and the use of new drugs that prevent rejection of transplanted organs. Transplant

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surgeons in Europe and in the United States have found cyclosporine A (Cy A), a potent immunosuppressive agent, to be at least as good as any of the conventional immunosuppressant regimens, and some researchers report dramatic improvements in patient and graft survival rates using the drug. However, interim analysis of an ongoing prospective randomized controlled clinical trial conducted by Dr. John S. Najarian and his associates at the University of Minnesota Medical School demonstrates no statistically significant differences in patient and graft survival when Cy A and conventional immunosuppressive regimens are compared.

The researchers also report that Cy A has been effective in decreasing the incidence of serious bacterial and viral infections in transplant patients. Future studies planned by this group will be aimed at understanding the biochemical effects of the drug at the cellular level in hopes of optimizing the efficacy of Cy A while minimizing its toxicity.

NIADDK grantee Dr. Bryan D. Myers and his associates at the Stanford University School of Medicine, Stanford, Calif., have found that prolonged treatment with Cy A can have deleterious effects on the kidney that can lead to irreversible kidney failure. In recent research, the scientists found that patients treated for a period of 12 to 24 months with Cy A lost about 50 percent of the filtering capacity of their kidneys. These investigators urge caution in the use of Cy A, and point to the need for development of safer protocols for long-term administration of the immunosuppressive agent.

Nutritional Therapy in Progressive Kidney Disease

Studies over the past several decades have indicated that dietary restriction of protein and/or phosphates may slow the rate of progression of several chronic renal disorders, retard kidney failure, and reduce the symptoms associated with renal diseases.

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In recent research, NIADDK grantee Dr. Mackenzie Walser and his associates at the Johns Hopkins University School of Medicine in Baltimore and the Brigham and Women's Hospital in Boston found that a low-protein, low-phosphorus diet supplemented with amino acids and keto acids markedly influenced the course of progressive chronic renal failure in 10 out of 17 patients studied. The investigators report that progression of the disease "has virtually been arrested for an average of 2 years to date" in seven of the patients who responded positively to the regimen.

The Institute continues to intensify its support of research on the influence of nutritional factors on the rate of progression of renal failure. The Chronic Renal Disease/Renal Transplantation Program currently is funding a multicenter cooperative clinical study to test the hypotheses that: (1) restriction of dietary protein reduces the rate of progression of chronic kidney disease in humans; and (2) it is nutritionally safe to restrict dietary protein in patients with progressive kidney failure. Dr. Walser and his associates indicate that if the results of their studies prove to be true in greater patient populations, and if progression of the disease in a large proportion of patients can be arrested for many years, "the need for dialysis will be substantially reduced."

Potassium Citrate for Kidney Stone Prevention

Research into the causes and mechanisms of stone formation is bringing about prevention of stone disease and far more effective clinical management than was possible just a few years ago. In previous research, grantee Dr. Charles Y.C. Pak and his associates at the University of Texas Health Science Center at Dallas discovered that the drug sodium cellulose phosphate (SCP) is particularly effective in controlling the recurrence of stones due to absorptive hypercalciuria, a specific condition in which the body absorbs too much calcium from food.

In a more recent 3-year trial funded by NIADDK, Dr. Pak and his colleagues investigated the long-term effects of another

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drug, potassium citrate, in patients with calcium kidney stones. Such stones can form when the urine contains low levels of citrate, with excessive levels of calcium and oxalate. The drug was effective in preventing new calcium stone formation in 75 to 91 percent of patients with stones in three different groups studied. The Food and Drug Administration has approved potassium citrate for investigation in the treatment of calcium stones.

Prevention of Kidney Damage Resulting From Urinary Tract Infection

Past studies by Dr. James A. Roberts and his associates at Tulane Medical School in New Orleans, La., have revealed the sequence of events following urinary tract infections that may lead to kidney infection (pyelonephritis) with renal scarring and loss of kidney function. Working in collaboration with Swedish scientists, Dr. Roberts and his colleagues identified specific bacteria with hair-like structures on their surface (P-fimbriated) that allow them to attach to cells of the urinary tract. Subsequently, bacterial toxins paralyze muscular functions of the ureter, infection spreads to the kidney, and white blood cells attack the bacteria by releasing toxic oxygen metabolites, causing loss of kidney tissue and function. Dr. Roberts and his associates recently have determined that P-fimbriated E. coli are associated with kidney infections, whereas non-P-fimbriated E. coli were found in patients with bladder infections.

New research by Dr. Lowell Parsons, University of California at San Diego, suggests that mucin (a glycoprotein that is the chief constituent of mucus) secreted by the mucous membrane of the urinary tract may be protective against infecting organisms, including some cancer-causing agents. Investigators point to the eventual development of new therapies based on these and other findings such as a drug to prevent attachment of the bacteria to the urinary tract cells, administration of the enzyme superoxide dismutase to decrease the effect of toxic oxygen metabolism, and immunization with purified fimbriae.

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HEMATOLOGY

The goal of research in hematology is to increase the fundamental and applied knowledge about blood and blood diseases. Major categories of this research effort are anemias of genetic origin, nutritional anemias, anemias associated with chronic diseases such as kidney failure and arthritis, disorders of blood cell production, metabolic disorders, and immunology. In addition, the availability of blood and blood cells facilitates study of membrane phenomena, protein structure and function, and other areas of research that provide information important to management of medical problems such as chronic renal insufficiency, transplantation, arthritis, nutritional disorders, and malignancy.

Blood diseases research is being spurred by remarkable advances in molecular genetics, which now holds hope for preventing or improving treatment of diseases of abnormal hemoglobin (the principal constituent of red blood cells), such as sickle cell disease and thalassemia, through chemical modification of defective genes or blood proteins. New techniques also permit more precise study of specific genes that control formation of the protein component of hemoglobin.

Prenatal Diagnostic Tests for Sickle Cell Anemia and Thalassemia

Institute grantee Dr. Yuet Wai Kan and his associates at the University of California in San Francisco have developed and refined a test for prenatal diagnosis of the severe genetic diseases sickle cell anemia and thalassemia. The new approach involves directly analyzing genetic material in cells from the amniotic fluid (the protective liquid that surrounds the fetus). This technique provides a safe, sensitive, and accurate method of diagnosing these genetic diseases. The method can be used as early as the 16th week of pregnancy. The researchers report that

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further refinements, currently under investigation, could make diagnosis possible during the first 12 weeks of pregnancy. The scientists point to future applications of this technology to other genetic disorders such as growth hormone defects, Huntington's disease, and Duchenne muscular dystrophy.

Sensitive, Nonradioactive Test Reveals Mild Iron Deficiency

Iron is essential to human life and depletion of the body's iron supply can result in iron-deficiency anemia. A new test (known as the small-dose iron tolerance test) has been developed that makes it possible to evaluate absorption of iron by the body without exposing the patient to radioactive tracers. NIADDK grantee William H. Crosby and his colleagues at the Walter Reed Army Institute of Research in Washington, D.C., found that small doses of iron given orally elevate the concentration of iron in blood plasma significantly and consistently in mildly iron-deficient subjects. The study demonstrates that increased iron absorption is a sensitive indicator of iron deficiency. The small-dose iron tolerance test may facilitate epidemiologic studies and provide important information concerning normal iron balance. The new test will allow physicians to evaluate the benefits of dietary supplements containing iron and to deal more effectively with numerous problems relating to iron metabolism in the body.

Noninvasive Magnetic "Biopsy" Aids Treatment of Iron Overload Disorders

Patients suffering from iron depletion anemia or from iron overload disorders (such as Cooley's anemia or hereditary hemochromatosis) have abnormal levels of body iron, which must be regulated. NIADDK grantee Dr. John Harris and his associates at the Case Western Reserve University School of Medicine in Cleveland have developed a magnetic device that can be used outside of the body to determine its iron content. At present, it is the only instrument of its kind in the world.

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The device will allow earlier identification of patients at risk of iron overload. Methods to assess the amount of body iron have depended until now on indirect, relatively insensitive techniques or invasive procedures such as liver biopsy. The new technique is direct, noninvasive, and more reliable, accurate, and practical than previous methods.

The instrument, known as a superconducting quantum-interference device (SQUID) susceptometer, is placed on the abdomen directly over the liver and measures its iron content in less than a minute. The liver is one of the main sites of body iron storage, and thus reflects the extent of iron accumulation by the body.

So far, about 200 patients have been tested with the instrument, and many more are expected to be referred for the test by physicians in the U.S. and abroad. Candidates include patients with Cooley's anemia, aplastic anemia, porphyria, and liver and kidney diseases, among other disorders.

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